

RECEIVED  
CENTRAL FAX CENTER  
JUL 08 2005

**THE WEBB LAW FIRM**

700 Koppers Building

436 Seventh Avenue

Pittsburgh, PA 15219-1818

Telephone: 412-471-8815 Facsimile: 412-471-4094

E-mail: webblaw@webblaw.com

**FACSIMILE INFORMATION SHEET**

RESPONSE UNDER 37 C.F.R §1.116  
EXPEDITED PROCEDURE  
GROUP ART UNIT 1617

Name of Individual: MAIL STOP AF  
Commissioner for Patents

Company: United States Patent and Trademark Office  
City and State: Alexandria, VA

Facsimile Number: 703-872-9306

From: Ann M. Cannoni, Esquire

Total Number of Pages: -10-

Date Transmitted: July 8, 2005

CV01379K US

Client No.: 4686

File No.: 045566

**Message:**

Application No. 10/057,646  
Inventors: Harry R. Davis  
Filed: January 25, 2002  
Title: COMBINATIONS OF NICOTINIC ACID AND DERIVATIVES THEREOF AND STEROL  
ABSORPTION INHIBITOR(S) FOR VASCULAR INDICATIONS

Transmittal Form (1p)  
Request for Reconsideration (8pp)

If you do not receive all pages, please call back as soon as possible. The number is (412) 471-8815.

**STATEMENT OF CONFIDENTIALITY**

The information in this facsimile is privileged and confidential and is intended only for the use of the named recipient. Disclosure or copying of this document or its contents other than by the named recipient is prohibited. If this document is received in error, it should be returned to sender.

If there are any reception problems, please call 412-471-8815.

PTO/SB/21 (04-04)

Approved for use through 07/31/2006. OMB 0851-0031


U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

<b>TRANSMITTAL FORM</b> (to be used for all correspondence after initial filing)	Application Number	10/057,648
	Filing Date	January 25, 2002
	First Named Inventor	Harry R. Davis
	Art Unit	1617
	Examiner Name	Shengjun Wang
Total Number of Pages in This Submission	9	Attorney Docket Number
		CV01378US/4886-045566

**ENCLOSURES (Check all that apply)**

<input type="checkbox"/> Fee Transmittal Form <input type="checkbox"/> Fee Attached <input checked="" type="checkbox"/> Amendment/Reply <input checked="" type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Documents <input type="checkbox"/> Response to Missing Parts/ Incomplete Application <input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53	<input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition to Reinstate <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s)_____	<input type="checkbox"/> After Allowance communication To Technology Center (TC) <input type="checkbox"/> Appeal Communication to Board Of Appeals and Interferences <input type="checkbox"/> Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input type="checkbox"/> Other Enclosure(s) (please identify below)
<b>Remarks</b>  		

Firm Or Individual name	Ann M. Cannoni The Webb Law Firm
Signature	
Date	July 8, 2005

**CERTIFICATE OF TRANSMISSION/MAILING**

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Typed or printed name	Chris Craig	Date	7/8/2005
Signature			

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing this form, call 1-800-PTO-9199 and select option 2.

RECEIVED  
CENTRAL FAX CENTER  
JUL 08 2005

Application No. 10/057,646  
Paper Dated: July 8, 2005  
Reply to Office Action of May 10, 2005

MAIL STOP AF

RESPONSE UNDER 37 C.F.R. § 1.116

EXPEDITED PROCEDURE EXAMINER  
GROUP ART UNIT 1617

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Patent Application of Harry R. Davis et al.	: PATENT APPLICATION
	:
Serial No.: 10/057,646	: Group Art Unit: 1617
	:
Filed: January 25, 2002	: Examiner: Shengjun Wang
	:
For: Combinations of Nicotinic Acid and Derivatives Thereof and Sterol Absorption Inhibitor(s) and Treatments for Vascular Indications	: Atty. Docket No.: CV01379K
	:

MAIL STOP AF  
Commissioner for Patents  
PO Box 1450  
Alexandria, VA 22313-1450

REQUEST FOR RECONSIDERATION

This Amendment is being submitted in response to the final Office

Action mailed on May 10, 2005.

I hereby certify that this correspondence is being transmitted via  
facsimile addressed to the Commissioner for Patents, P.O. Box 1450,  
Alexandria, VA 22313-1450, facsimile number 703-872-9306 on July  
8, 2005

Chris Craig

(Name of Person Faxing Paper)

Signature

7/8/2005

Date

{W0199704.1}

Application No. 10/057,846  
Paper Dated: July 8, 2005  
Reply to Office Action of May 10, 2005

2

Claims 1-4, 7-10, 28-30 and 32 are pending in the application. Claims 11-27, 36-39, 41, 44-46, 51, 54, 56, 59, 61, 64, 66, 69, 72, 75, 78 and 81 have been withdrawn from consideration by the Examiner as being non-elected. Claims 5, 31 and 33-81 were previously canceled without prejudice to filing one or more divisional applications directed to the subject matter thereof. Claim 6 was canceled without prejudice to filing one or more divisional applications directed to the subject matter thereof.

At pages 2-6 of the Office Action, claims 1-4, 7-10, 28-30 and 32 have been rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 5,846,966 ("Rosenblum et al.") in view of U.S. Patent No. 5,698,527 ("Kim") and WO 2000/38725 ("Keller et al.").

In the rejection, it is asserted that Rosenblum et al. teach the claimed cholesterol absorption inhibitors, their application in lowering cholesterol and combination with other cholesterol lowering agents such as simvastatin. Also, it is alleged that Rosenblum et al. teach a daily dosage of such compounds when used in combination with another drug of about 1 mg to 1000 mg given 1 or 2 times a day. It is expressly acknowledged that Rosenblum et al. do not teach a combination of cholesterol absorption inhibitor and nicotinic acid.

In the rejection, it is alleged that Kim teaches that niacin is a well-known cholesterol lowering agent and is particularly useful in combination with cholesterol absorption inhibitors. It is further alleged that Keller et al. teach various combinations of cholesterol lowering agents, including ezetimibe and nicotinic acid, for treating hypercholesterolemia-associated disorders.

{W0199704.1}

2

Application No. 10/057,646  
Paper Dated: July 8, 2005  
Reply to Office Action of May 10, 2005

3

It is alleged that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising ezetimibe and nicotinic acid, and optionally simvastatin, since the compounds are known for use for the same purpose, citing In re Kerkoven. As to the specific amount, it is argued that they amount is within the disclosed range.

Applicants respectfully traverse this rejection and request that the rejection be reconsidered and withdrawn.

When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a prima facie case of obviousness. In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992).

The Examiner can satisfy this burden only by showing an objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, which would lead an individual to combine the relevant teachings of the references [and/or the knowledge] in the manner suggested by the Examiner. Id.; In re Fine, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The mere fact that the prior art could be modified does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 U.S.P.Q.2d at 1784; In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989); In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

"It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious....[o]ne cannot use hindsight

{W0199704.1}

3

Application No. 10/057,646  
Paper Dated: July 8, 2005  
Reply to Office Action of May 10, 2005

4

reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.” In re Fritch, 23 U.S.P.Q.2d at 1784 (quoting In re Fine, 5 U.S.P.Q.2d at 1600).

“The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence.” Manual of Patent Examining Procedure, (Rev. 1, Feb. 2003) § 716.01(d) and In re Oetiker, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

As shown in Table 1 of the present application, Compound XII (a substituted azetidinone cholesterol absorption inhibitor) reduced plasma cholesterol levels and the accumulation of hepatic cholesteryl esters in the cholesterol-fed hamsters. Niacin reduced plasma triglyceride levels, but did not significantly reduce the cholesterol levels. The combination of Compound XII and niacin resulted in reductions in plasma and hepatic cholesterol levels, as well as plasma triglycerides (Table 1). These results indicate that the combination of the cholesterol absorption inhibitor of Compound XII and niacin can have additive effects on treating hyperlipidemia in male Golden Syrian hamsters, by reducing both cholesterol and triglyceride levels. As is well known to those skilled in the art, the efficacy of combinations of drug compounds can be unpredictable.

Rosenblum et al. do not suggest or disclose the combination of ezetimibe and nicotinic acid. Rosenblum et al. do not suggest or disclose the desirability of a 10 milligram dosage of ezetimibe.

{W0199704.1}

4

Application No. 10/057,646  
Paper Dated: July 8, 2005  
Reply to Office Action of May 10, 2005

5

Kim discloses steroidal glycoside cholesterol absorption inhibitors that can be administered in combination with niacin, but does not suggest or disclose combining ezetimibe with niacin or the desirability of the claimed amount of 10 milligrams of ezetimibe. Ezetimibe is not a steroidal glycoside. The steroidal glycosides disclosed by Kim are structurally very dissimilar to the presently claimed substituted azetidinone compound ezetimibe. Given their large molecular size, it is unlikely that Kim's steroidal glycosides are absorbed through the intestine. In contrast, multiple peaks in plasma concentration-time profiles suggest that the glucuronide conjugate of ezetimibe undergoes enterohepatic recycling before elimination. See ZETIA™ (ezetimibe) Tablets Package Insert at column 2 (Merck/Schering-Plough Pharmaceuticals) (October 2002), included in the Information Disclosure Statement of August 30, 2004. This enterohepatic recycling can enhance efficacy. It would not be obvious to one of ordinary skill in the art to substitute ezetimibe disclosed by Rosenblum et al. for the steroidal glycosides disclosed by Kim, since they are likely to be dissimilar in site of action.

Kim's steroidal glycoside compounds have not been commercialized by Merck & Co., Inc. (the assignee of the Kim patent). Rather, Merck is the joint venture partner of Schering-Plough (assignee of the present application) in marketing the cholesterol absorption inhibitor ZETIA™ ezetimibe formulation. ZETIA was launched in late 2002 and global sales of ZETIA in the 2003 fourth quarter totaled \$165 million, with U.S. sales of \$144 million. Press Release: Schering-Plough Reports Financial Results for 2003 Fourth Quarter,

{W0199704.1}

5

Application No. 10/057,648  
Paper Dated: July 8, 2005  
Reply to Office Action of May 10, 2005

6

Full Year (Monday January 26, 6:33 am ET). Thus it can be inferred that Kim's steroidal glycoside compounds were not commercially viable as treatments.

"[S]econdary considerations such as ... commercial success, long-felt need, failure of others ... are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence." M.P.E.P. § 2141 (Rev'd May 2004). Applicants respectfully request that the above information regarding commercial success, long-felt need, and failure of others be considered by the Examiner.

No data is presented in the Kim reference to support efficacy of a combination of steroidal glycoside and niacin. One skilled in the art would not be motivated to combine ezetimibe and nicotinic acid based upon the disclosure of Kim since the steroidal glycoside and ezetimibe molecules are so structurally dissimilar.

Keller et al. disclose combinations of (1) an ileal bile acid transport inhibitor or CETP inhibitor and (2) a cholesterol absorption inhibitor such as ezetimibe, but *not the combination of ezetimibe and nicotinic acid*. Also, Keller does not suggest or disclose the desirability of a 10 mg dosage of ezetimibe.

It is respectfully submitted that the combination of the references cited as rendering the claimed invention obvious is improper because there is no suggestion in the cited references to combine the claimed components of 10 milligrams of ezetimibe and nicotinic acid.

{W0199704.1}

6



Application No. 10/057,646  
Paper Dated: July 8, 2005  
Reply to Office Action of May 10, 2005

7

Even if the teachings of the references were combined as set forth in the Office Action, there are not sufficient teachings to motivate one of ordinary skill in the art to combine 10 milligrams of ezetimibe with nicotinic acid.

Neither Rosenblum et al, Kim, nor Keller et al., taken alone or combined as set forth in the Office Action, provides motivation for combining 10 milligrams of ezetimibe and niacin. Also, Applicants respectfully request that the above information regarding commercial success, long-felt need, failure of others be considered by the Examiner. Accordingly, reconsideration and withdrawal of the §103(a) rejection is respectfully requested.

Applicants respectfully request that the Examiner return an initialed PTO-1449 form for the Information Disclosure Statement submitted herewith and each of the Information Disclosure Statements submitted on October 28, 2003, April 12, 2004 and May 13, 2004, indicating that the Examiner has considered each of the references cited therein.

In view of the foregoing remarks, it is respectfully submitted that all of the pending claims in the present application are distinguishable from the cited

{W0199704.1}

7

Application No. 10/057,646  
Paper Dated: July 8, 2005  
Reply to Office Action of May 10, 2005

8

prior art. Accordingly, reconsideration and withdrawal of the rejection and an early Notice of Allowance are respectfully requested.

Respectfully submitted,

Date: July 8, 2005



Ann Marie Cannoni

Registration No. 35,972

The Webb Law Firm.  
700 Koppers Building  
436 Seventh Avenue  
Pittsburgh, PA 15219  
Phone: (412) 471-8815  
Fax: (412) 471-4094  
E-mail: [acannoni@webblaw.com](mailto:acannoni@webblaw.com)

(WO199704.1)

8